



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: WO 98/07850 (11) International Publication Number: C12N 15/12, C07K 14/47, C12Q 1/68, **A2** (43) International Publication Date: 26 February 1998 (26.02.98) G01N 33/50 PCT/EP97/04599 (81) Designated States: AU, CH, CN, JP, NO, NZ, RU, US, (21) International Application Number: European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, (22) International Filing Date: GR, IE, IT, LU, MC, NL, PT, SE). 22 August 1997 (22.08.97) (30) Priority Data: **Published** 22 August 1996 (22.08.96) CA Without international search report and to be republished 2,183,901 upon receipt of that report. (71)(72) Applicants and Inventors: BERGMANN, Johanna, E. [DE/DE]; Mörikestrasse 22, D-22587 Hamburg (DE). PREDDIE, Enrique, R. [CA/CA]; 4875 Dufferin Street, Montreal, Quebec H3X 2Z2 (CA).

(54) Title: AGENTS FOR PRE-SYMPTOMATIC DETECTION AND THERAPEUTIC TARGETING OF ALZHEIMER'S DISEASE AND DOWN SYNDROME IN HUMANS

(57) Abstract

Agents and methods for the diagnosis and therapy of Alzheimer's disease and the related condition Down syndrome are disclosed. Such agents include four genes located within the region of human chromosome 21 occupied by the APP gene, which are exclusively expressed in Alzheimer's disease or Down syndrome, respectively, the proteins encoded and expressed by these genes, the nucleic acid molecules influencing their expression, and endogenous antibodies produced in humans with Alzheimer's disease and Down syndrome against the above proteins. Also disclosed are antibodies and nucleotides to detect the presence of the proteins and nucleic acids in humans.

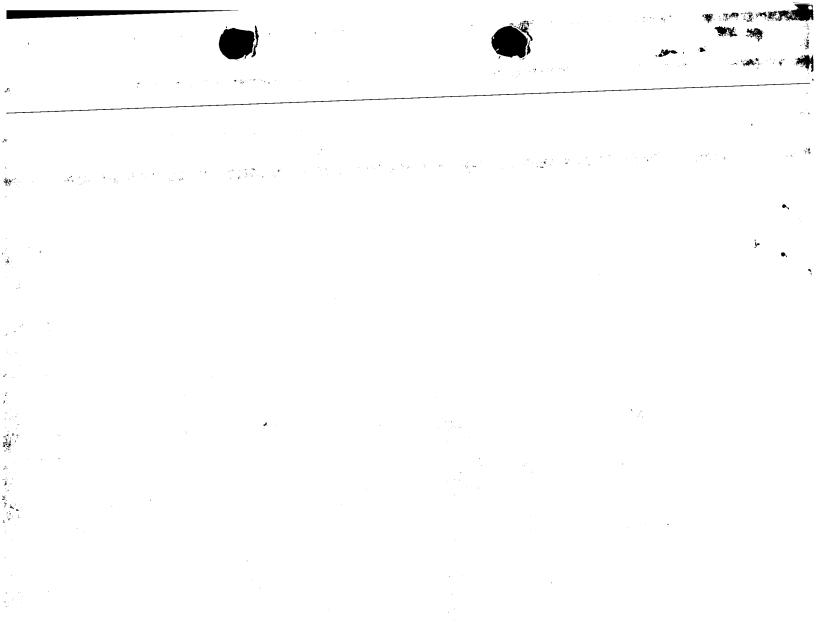
.5.

•

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia . |
|------|--------------------------|----|---------------------|----|-----------------------|-----------|--------------------------|
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| ΑU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| ΑZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | СH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | | Republic of Macedonia | TR | Turkey |
| BG . | Bulgaria | HU | Hungary | ML | Mali | TT | Trinidad and Tobago |
| ВJ | Benin | ΙE | Ireland | MN | Mongolia | UA | Ukraine |
| BR | Brazil | IL | Israel | MR | Mauritania | UG | Uganda |
| BY | Belarus | IS | Iceland | MW | Malawi | US | United States of America |
| CA | Canada | IT | Italy | MX | Mexico | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NE | Niger | VN | Viet Nam |
| CG | Congo | KE | Kenya | NL | Netherlands | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NO | Norway | zw | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's | NZ | New Zealand | | |
| CM | Cameroon | | Republic of Korea | PL | Poland | | |
| CN | China | KR | Republic of Korea | PT | Portugal | | |
| CU | Cuba | KZ | Kazakstan | RO | Romania | | |
| CZ | Czech Republic | LC | Saint Lucia | RU | Russian Federation | | |
| DE | Germany | LI | Liechtenstein | SD | Sudan | | |
| DK | Denmark | LK | Sri Lanka | SE | Sweden | | |
| EE | Estonia | LR | Liberia | SG | Singapore | | |
| | | | | | | | |



PCT





INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C12N 15/12, 15/55, 9/64, C07K 14/47, C12Q 1/68, G01N 33/50, A61K 38/17, 38/46, C12N 15/85, C07K 14/705

A3

(11) International Publication Number:

WO 98/07850

(43) International Publication Date:

26 February 1998 (26.02.98)

(21) International Application Number:

PCT/EP97/04599

(22) International Filing Date:

22 August 1997 (22.08.97)

(30) Priority Data:

2,183,901

22 August 1996 (22.08.96)

CA

(71)(72) Applicants and Inventors: BERGMANN, Johanna, E. [DE/DE]; Mörikestrasse 22, D-22587 Hamburg (DE). PREDDIE, Enrique, R. [CA/CA]; 4875 Dufferin Street, Montreal, Quebec H3X 2Z2 (CA).

(81) Designated States: AU, CH, CN, JP, NO, NZ, RU, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

With international search report.
With amended claims and statement.

(88) Date of publication of the international search report: 17 September 1998 (17.09.98)

Date of publication of the amended claims and statement: 5 November 1998 (05.11.98)

(54) Title: AGENTS FOR PRE-SYMPTOMATIC DETECTION AND THERAPEUTIC TARGETING OF ALZHEIMER'S DISEASE AND DOWN SYNDROME IN HUMANS

(57) Abstract

Agents and methods for the diagnosis and therapy of Alzheimer's disease and the related condition Down syndrome are disclosed. Such agents include four genes located within the region of human chromosome 21 occupied by the APP gene, which are exclusively expressed in Alzheimer's disease or Down syndrome, respectively, the proteins encoded and expressed by these genes, the nucleic acid molecules influencing their expression, and endogenous antibodies produced in humans with Alzheimer's disease and Down syndrome against the above proteins. Also disclosed are antibodies and nucleotides to detect the presence of the proteins and nucleic acids in humans.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | . I Lagrining | AIRCITIATIONA. | applications under the |
|--|--|--|---|---|--|--|---|
| AL AM AT AU AZ BA BB BE BF BG BJ BR CA CF CG CH CI CM CN CU CZ DE DK | Albania Armenia Austria Australia Azerbaijan Bosnia and Herzegovina Barbados Belgium Burkina Faso Bulgaria Benin Brazil Belarus Canada Central African Republic Congo Switzerland Côte d'Ivoire Cameroon China Cuba Czech Republic Germany Denmark | ES FI FR GA GB GE GH GN GR HU IE IL IS IT JP KE KG KP KR LC LI | Spain Finland France Gabon United Kingdom Georgia Ghana Guinea Greece Hungary Ireland Israel Iceland Italy Japan Kenya Kyrgyzstan Democratic People's Republic of Korea Republic of Korea Kazakstan Saint Lucia Liechtenstein | LS LT LU LV MC MD MG MK ML MN MR MW MX NE NL NO NZ PL PT RO RU SD | Lesotho Lithuania Luxembourg Latvia Monaco Republic of Moldova Madagascar The former Yugoslav Republic of Macedonia Mali Mongolia Mauritania Malawi Mexico Niger Netherlands Norway New Zealand Poland Portugal Russian Federation Sudan | SI SK SN SZ TD TG TJ TM TR TT UA UG US UZ VN YU ZW | Slovenia Slovakia Senegal Swaziland Chad Togo Tajikistan Turkey Trinidad and Tobago Ukraine Uganda United States of America Uzbekistan Viet Nam Yugoslavia Zimbabwe |

SE

 \mathbf{SG}

Sudan

Sweden

Singapore

Sri Lanka

Liberia

LK

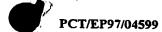
LR

DE DK

EE

Denmark

Estonia



AMENDED CLAIMS

[received by the International Bureau on 16 September 1998 (16.09.98); original claims 1-25 replaced by amended claims 1-10 (2 pages)]

- (1) Specific ELISA methods for presymptomatic diagnosis of Downs syndrome in humans; this involves detecting, in extracts from human skin cells, serum, plasma and saliva, a Downs syndrome specific marker "DSAS", "SEQ ID:NO3" or the DSAS-containing protein "PAC", "SEQ ID:NO10"
- (2) A specific ELISA method of claim 1 which detects endogenous antibodies produced in humans body fluids against DSAS, SEQ ID:NO3 and/or PAC, SEQ ID:NO10. The endogenous antibody is detected in all humans afflicted with Downs syndrome, in humans before any clinical symptoms of Downs symptoms appear and also in mothers carrying Downs syndrome babies.
- (3) A method for preventing and treating Downs syndrome in humans that targets dsas, SEQ ID:NO1; pac, SEQ ID:NO9; DSAS, SEQ ID:NO3; PAC, SEQ ID:NO10; anti-DSAS endogenous antibody or anti-PAC endogenous antibody.
- (4)Methods for presymptomatic diagnosis of all forms of Alzheimer's disease and clinically related conditions in humans that involve detecting in human cells, tissue and/or body fluids (serum, plasma, spinal fluid, saliva) mRNA, "alzas", SEQ ID:NO11 (specifically 204-241) or, m**RN**A "alzas1", SEQ ID: NO15 (specifically 55-1**5**6) mRNA "alzas2". or, SEO ID: NO24 (specifically nucleotides 97-132).
- (5) The method of claim 4 which detects the proteins "ALZASP", SEQ ID:NO12 expressed by alzas (SEQ ID:NO11) specifically amino acids 68 79 which are encoded by alzas nucleotides 204 241 or the protein "ALZAS1", SEQ ID:NO16 expressed by alzas1 (SEQ ID:NO15) specifically amino acid 20-51 which are encoded by alzas1 nucleotides 55-156 or "ALZAS2" (SEQ ID:NO25) expressed by alzas2 (SEQ ID:NO24) especially amino acids 33-44 which are encoded by alzas2 nucleotides 97-132.
- (6) The amino acid sequences of claim 5 wherein these sequences are amino acid residues 68-79 from SEQ ID:NO11; amino acid residues 20-51 from SEQ ID:NO16 and amino acid residues 33-44 from SEQ ID:NO25.
- (7) A method of claim 4 that detects an endogenous antibody produced in humans about to become afflicted or already afflicted with Alzheimer's disease, that is directed against epitopes within the amino acid residues of claim 6.

- (8) Methods for preventing, controlling and treating Alzheimer's disease and other closely related clinical condition in humans that involve, blocking transcription of mRNA molecules from the group of claim 4 which have the sequence ID numbers SEQ ID:NO11, SEQ ID:NO15 and SEQ ID:NO24, specifically nucleotides 204-241, 55-156 and 97-132 respectively, or preventing the expression of or activity of the proteins of claims numbers 5 and 6, or preventing the activity of the endogenous antibodies of claim 7.
- (9) A method of claim 5 which detects the proteins of the group "hyp1(ALZASP)" SEQ ID:NO13, "hyp2(ALZASP)" SEQ ID:NO14 and "hyp(ALZAS2)" SEQ ID:NO26 in humans about to be afflicted or afflicted with Alzheimer's disease or associated clinical conditions.
- (10) The methods of claim 8 which involves preventing the expression or activity of the proteins of claim 9, and activity of the anti-endogenous antibody directed against these proteins when they are expressed in humans afflicted with Alzheimer's disease and closely related clinical conditions.



STATEMENT UNDER ARTICLE 19

In our view the amended claims have no significant impact on the description or the drawings of the present application; however, changes in the latter which might be deemed necessary by others will be done during the preliminary examination phase of the application. A copy of this letter and the amended claims are being sent simultaneously to the International Preliminary Examining Authority.

